UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/708,786 | 11/08/2000 | Sudhir Agrawal | 47508.700 | 2469 |

23483 7590 04/17/2006

WILMER CUTLER PICKERING HALE AND DORR LLP
60 STATE STREET
BOSTON, MA 02109

| EXAMINER | |
|---|---|
| GIBBS, TERRA C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/708,786 | AGRAWAL, SUDHIR | |
| | Examiner | Art Unit | |
| | Terra C. Gibbs | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *January 30, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,5,6,8-11,14,15,17-20,23,24,26,27 and 29-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8-11,14,15,17-20,23,24,26,27 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed January 30, 2006.

Claims 1, 10, and 19 have been amended.

Claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, 27, 29-34 are pending in the instant application.

Claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, 27, 29-34 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 112*

In the previous Office Action mailed October 5, 2005, claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 14, and 29-34 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection is withdrawn** in view of Applicant's Amendment filed January 30, 2006 to recite, "about 5 to about 15 nucleotides or from about 13 to about 100 nucleotides" and to recite, "wherein statistical significance is determined using an unpaired t-test and p is less than 0.08". It is noted that instant specification has support for these recitations at pages 8 and 14, respectively.

In the previous Office Action mailed October 5, 2005, claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 14, and 29-34 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for statistically significantly potentiating the activity of an SN-38 prodrug by a p value of less than 0.08 in an unpaired t-test, comprising co-administering an oligonucleotide that is from about 13 to about 100 nucleotides in length with the prodrug, wherein the prodrug is administered at a dose of 50 mg/kg and the oligonucleotide is administered at a dose of 20 mg/kg, does not reasonably provide enablement for a method for statistically significantly potentiating the activity of an SN-38 prodrug by a p value of less than or equal to 0.08 in an unpaired t-test, comprising co-administering an oligonucleotide that is from about 5 to about 100 nucleotides in length with the prodrug. **This rejection is withdrawn** in view of Applicant's traversal filed January 30, 2006. Specifically, the Examiner has been persuaded by Applicant's arguments that it would not require undue experimentation to determine the range of doses of the oligonucleotide and the prodrug that would provide the claimed potentiating effect because such determination is routine in the art.

After careful reconsideration of the claims, new grounds of rejection(s) and/or observations are presented as follows:

***Nucleotide and/or Amino Acid Sequence Disclosure***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1)

and (a)(2). However, this application fails to comply with the requirements of 37 1.821 through 1.825 for the reason(s) set forth below. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 Fed. Reg. 18230, May 1, 1990. It is noted that the application fails to comply with 37 CFR 1.821(d).

It is noted that in the Amendment filed December 19, 2002, the specification was amended to include sequence identifiers (SEQ ID NOs.) at pages 8, 12, and 15. However, in the Amendment filed October 18, 2004, pages 12 and 15 were further amended where appropriate SEQ ID NOs. were not indicated. Given the replacement paragraphs made to the specification in the Amendment filed October 18, 2004, the sequences listed at pages 12 and 15 must have accompanying SEQ ID NOs.

The above is an example and is not intended to indicate that the Examiner has made an exhaustive review of the application. Applicant must fully comply with the sequence rules for any response to this action to be considered fully responsive.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, 27, 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koike et al. (Cancer Research, 1997 Vol. 57:5475-5479) in view of Miraglia et al. [U.S. Patent No. 6,184,212 B1].

Claim 1, 10, and 19 are drawn to a method for statistically significantly potentiating the activity of an SN-38 prodrug, the method comprising co-administering an oligonucleotide that is from about 5 to about 15 or from about 13 to about 100 nucleotides in length with the prodrug, wherein the oligonucleotide does not have two 5' and four 3' 2-0-methyribonucleosides, wherein the oligonucleotide does not have the sequence of SEQ ID NO:1, and wherein statistical significance is determined using an unpaired t-test and p is less than 0.08 when compared to a control. Claims 2, 5, 6, 8, 9, 11, 14, 15, 17, 18, 20, 23, 24, 26, 27, 29-34 depend from either claims 1, 10, or 19 and include all the limitations of claims 1, 10, or 19 with the further limitations wherein the prodrug is an ester or an amide of SN-38; wherein the prodrug is irinotecan; wherein the oligonucleotide comprises phosphorothioates, phosphorodithioates, or 2'-O-substituted ribonucleoside linkages.

It is noted that irinotecan is also known as Camptosar or CPT-11. It is further noted that SEQ ID NO:1 of the instant invention is an antisense oligonucleotide, 20 nucleotides in length, targeted and complementary to mdm-2.

Koike et al. teach the enhancement of drug sensitivity comprising combination therapy in which an SN-38 prodrug, specifically CPT-11, is administered with an oligonucleotide. Koike et al. teach an antisense cDNA enhances drug sensitivity in HepG2 cells treated with CPT-11. For example, Koike et al. teach HepG2 cells

transfected with a cMOAT antisense cDNA are more sensitive to CPT-11 than cells not transfected with the antisense cDNA (see Table 1 at HV1, HA6, or HA7). It is noted that the HepG2 cells were first transfected with the antisense cDNA and then treated with CPT-11 at an $IC_{90}$ concentration of 2.0 μg/ml (see Table 1).

Koike et al. do not teach wherein the oligonucleotide is from about 5 to about 15 or from about 13 to about 100 nucleotides in length, or wherein the oligonucleotide comprises phosphorothioates, phosphorodithioates, or 2'-O-substituted ribonucleoside linkages.

Miraglia et al. teach the inhibition of human mdm-2 gene expression in cells using antisense oligonucleotides, 20 nucleotides in length, targeted and complementary to human mdm-2 (see Abstract and claims). Specifically, Miraglia et al. teach the design of over several dozen antisense oligonucleotides targeted to mdm-2 (see Tables 1, 10, and 11). The antisense oligonucleotides taught by Miraglia comprise phosphorothioates, phosphorodithioates, or 2'-O-substituted ribonucleoside linkages (see Tables 1, 7, 10, and 11).

The burden of establishing whether the prior art oligonucleotide and SN-38 prodrug [as taught by Koike et al. and Miraglia et al.] has the further function of "statistically significantly potentiating the activity of the prodrug" under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195

USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the combination of the teachings of Koike et al. and Miraglia et al. would or would not have the additional functional limitation of "statistically significantly potentiating the activity of the prodrug" as instantly claimed.

Simply put, the instant claims are drawn to a method of combination therapy in which an SN-38 prodrug is administered with an oligonucleotide, resulting in the potentiation of antitumor activity of the prodrug by the oligonucleotide. It would have been *prima facie* obvious to one of ordinary skill in the art to devise a method for statistically significantly potentiating the activity of an SN-38 prodrug, the method comprising co-administering an oligonucleotide using the method taught by Koike et al. It would have been further obvious to devise a method of combination therapy in which an SN-38 prodrug is administered with an oligonucleotide since it is routine and well

known in the art that combination therapy is an effective and seemingly synergistic approach for cancer treatment.

One of ordinary skill in the art would have been motivated to make the oligonucleotide from about 5 to about 15 or from about 13 to about 100 nucleotides in length for use in a method for statistically significantly potentiating the activity of an SN-38 prodrug for ease of synthesis and delivery to cells in culture since it is well known in the art that longer antisense oligonucleotides, such as the one taught by Koike et al., are difficult to transfect *in vitro*. One of ordinary skill in the art would have been further motivated to make the oligonucleotide from about 5 to about 15 or from about 13 to about 100 nucleotides in length for use in a method for statistically significantly potentiating the activity of an SN-38 prodrug because it is conventional in the art to make antisense oligonucleotides within this size range (as exemplified by Miraglia et al.). One of ordinary skill in the art would have been motivated to modify the oligonucleotide for use in a method for statistically significantly potentiating the activity of an SN-38 prodrug since Miraglia et al. taught modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

One of ordinary skill in the art would have expected success at making the oligonucleotide from about 5 to about 15 or from about 13 to about 100 nucleotides in length or modifying the oligonucleotide for use in a method for statistically significantly potentiating the activity of an SN-38 prodrug since Miraglia et al. teach the successful

design and synthesis of over several dozen modified and unmodified antisense oligonucleotides targeted to mdm-2.

Therefore, the invention of claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, 27, 29-34 would have been *prima facie* obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
April 13, 2006